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EXAMINER
STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
1656	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/24/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/652,928	CHIAUR ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,11,13,14 and 16-36* is/are pending in the application.

4a) Of the above claim(s) *1-6,11 and 17-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7,13,14,16 and 29-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/8/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 1-7, 11, 13-14, and 16-36 pending in the application.

[2] Applicant's amendment to the claims, filed on 2/8/07, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[3] Applicant's amendment to the specification, filed on 2/8/07, is acknowledged.

[4] Receipt of an information disclosure statement, filed on 2/8/07, is acknowledged.

[5] Receipt of a substitute sequence listing in computer readable form (CRF), a paper copy thereof, a statement of their sameness, and a statement that no new matter has been added to the specification by the paper copy of the sequence CRF, all filed on 2/8/07, is acknowledged.

[6] Applicant's arguments filed on 2/8/07 in response to the Office action mailed on 8/8/06 have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[7] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Restriction/Election

[8] Claims 1-6, 11, and 17-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable

generic or linking claim. Election was made without traverse in the reply filed on 6/12/2006.

Information Disclosure Statement

[9] All references cited in the IDS filed on 2/8/07 have been considered by the examiner. References C59 and C78 have been lined through as these references were cited on Form PTO-892 attached to the Office action mailed on 8/8/06.

Sequence Compliance

[10] In order to perfect sequence compliance, applicant should submit an amendment to the specification directing entry of the sequence listing paper copy filed on 2/8/07.

Claim Rejections - 35 USC § 112, Second Paragraph

[11] The rejection of claims 7, 13-14, 16, and 29-36 under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation of "FBP1" and "βTrcp2" is maintained for the reasons of record and the reasons stated below.

RESPONSE TO ARGUMENT: Applicant argues at p. 13, middle that the specification makes clear that the term "FBP" is synonymous with "F-box protein," referring to a protein with an F-Box motif and includes those gene products encoded by SEQ ID NO:1 and nucleic acids that hybridize thereto under stringent conditions. Applicant argues the "FBP1" and "βTrcp2" proteins have a "specific and required activity," namely that of an F box protein subunit that targets IKBα for degradation.

According to applicant, in order for the species of FBP1 or βTrcp2 proteins to exhibit such function, the proteins "must be structurally similar." According to applicant, the specification teaches an FBP gene comprises any DNA sequence that hybridizes to the complement of a DNA encoding an FBP protein, such as FBP1, hybridizing variants thereof that encodes a "functionally equivalent" protein. Applicant argues that "not all sequences that hybridize to the complement of SEQ ID NO:1 are encompassed by the claims – only those that target IKBα for degradation." Applicant further argues DNA sequences of βTrcp2 isoforms were known in the prior art and one of skill in the art would know that not "minor variations" will still yield functional βTrcp2 species.

Applicant's argument is not found persuasive. While applicant argues the scope of "FBP1" and "βTrcp2" proteins has the function of targeting IKBα for degradation and the scope of FBP1 proteins is structurally limited to those encoded by SEQ ID NO:1 and hybridizing variants thereof or βTrcp2 with "minor variations," it is noted that the claims do not appear to so limit the function and structure of the members of the genus. MPEP 2111.01.II states, "it is important not to import into a claim limitations that are not part of the claim." Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Indeed, the specification discloses "[f]unctionally equivalent FBP gene products may contain deletions,...additions,...or substitutions of amino acid residues within...the amino acid sequence encoded by the FBP gene" (p. 40, lines 8-10) and that "where alteration of function is desired, deletions or non-conservative alterations can be engineered to produce altered FBP gene

products. Such alterations can, for example, alter one or more of the biological functions of the FBP gene product" (p. 40, lines 20-22). According to MPEP 2111.01.I, "[d]uring examination, the claims must be interpreted as broadly as their terms reasonably allow." The specification initially sets forth a narrow "definition" of "Fbp1" or "βTrcp2" (specification at p. 4, line 22 to p. 5, line 26) and then broadly defines these terms as having essentially any structure and any function (specification at p. 40). Moreover, applicant asserts the scope of "Fbp1" or "βTrcp2" is intended to encompass proteins that fall between these narrow and broad descriptions of the terms. Further, as noted in the prior Office action, the prior art recognizes at least two other proteins as "Fbp1" that appear to be structurally and functionally distinct from the "Fbp1" protein described in the specification. Furthermore, the specification and prior art acknowledge the existence of multiple FBP proteins and it is unclear as to how a skilled artisan distinguishes an "FBP1" protein from other FBP proteins, *e.g.*, "FBP2," "FBP3," "FBP4," etc.

At least for the reasons of record and the reasons stated above, a skilled artisan would not be able to recognize the intended scope of proteins encompassed by the terms "Fbp1" or "βTrcp2."

[12] Claims 14, 16, 30, 32, 34, and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 (claims 16, 30, 32, 34, and 36 dependent therefrom) is confusing in the recitation of "the FBP1 or βTrcp2 activity comprises degradation of IKBα." While the specification acknowledges the activity of FBP1 or βTrcp2 as interacting with IKBα (see, *e.g.,* instant response at p. 14, middle) and applicant's instant response acknowledges that an activity of FBP1 or *β*Trcp2 is promoting degradation of IKBα (see instant response at p. 14, middle), there is no indication that the activity of FBP1 or *β*Trcp2 is degradation of IKBα. It is suggested that applicant clarify the meaning of the claim.

Claim Rejections - 35 USC § 112, First Paragraph

[13] Claims 7, 13-14, 16, and 29-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 14 has been amended to recite, "the FBP1 or *β*Trcp2 activity comprises degradation of IKBα." According to the instant response at p. 12, top, support for this limitation can be found at pp. 9-10, 29-30,59-60, and 62. MPEP § 2163 states, "when filing an amendment an applicant should show support in the original disclosure for new or amended claims" (MPEP 8th Ed., October 2006 Revision at pp. 2100-176 and 2100-183).and "[i]f the originally filed disclosure does not provide support for each claim limitation, or if an element which applicant describes as essential or critical is not

claimed, a new or amended claim must be rejected under 35 U.S.C. 112, para. 1, as lacking adequate written description." The examiner has carefully reviewed applicant's cited support for the noted limitation. However, the examiner can find no support for an activity of FBP1 or βTrcp2 being degradation of IKBα. Applicant is invited to "show support" for the limitation at issue in accordance with MPEP 2163.

[14] The written description rejection of claims 7, 13-14, 16, and 29-36 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a prior Office action.

RESPONSE TO ARGUMENT: Addressing the genus of FBP1 and βTrcp2 proteins, applicant argues the genus of proteins have a "specific and required activity," namely that of an F box protein subunit that targets IKBα for degradation. According to applicant, in order for the species of FBP1 or βTrcp2 proteins to exhibit such function, the proteins "must be structurally similar." Applicant argues the structural features of F box proteins that are determinant of function "had been extensively studied and were well known in the art" and the specification discloses methods for detecting FBP1 and βTrcp2 activity. According to applicant, the specification teaches the FBP1 gene comprises SEQ ID NO:1, any nucleic acid encoding SEQ ID NO:2, and hybridizing variants thereof. Applicant argues that "not all sequences that hybridize to the complement of SEQ ID NO:1 are encompassed by the claims – only those that target IKBα for degradation." Applicant further argues DNA sequences of βTrcp2 isoforms were known in the prior art. According to applicant, one of skill in the art would not expect substantial variation among members of the genus of nucleic acids "because the

hybridization conditions as set forth in the claims would yield structurally similar FBP1 proteins," relying on Example 9 of the Written Description Guidelines.

Applicant's argument is not found persuasive. While applicant argues the genus of FBP1 and βTrcp2 proteins has the function of targeting IKBα for degradation and the genus is structurally limited to FBP1 proteins encoded by SEQ ID NO:1, any nucleic acid encoding SEQ ID NO:2, and hybridizing variants thereof or βTrcp2 with "minor variations," it is noted that the claims do not appear to so limit the function and structure of the members of the genus. Indeed, in view of the disclosure of the specification, a skilled artisan would recognize the terms "FBP1" and "βTrcp2" are neither structurally nor functionally limited or "conventional or well known to one of skill in the art." For example, the specification discloses "[f]unctionally equivalent FBP gene products may contain deletions,...additions,...or substitutions of amino acid residues within...the amino acid sequence encoded by the FBP gene" (p. 40, lines 8-10) and that "where alteration of function is desired, deletions or non-conservative alterations can be engineered to produce altered FBP gene products. Such alterations can, for example, alter one or more of the biological functions of the FBP gene product" (p. 40, lines 20-22). According to MPEP 2111.01.I, "[d]uring examination, the claims must be interpreted as broadly as their terms reasonably allow." As such, the term "FBP1" has been broadly, but reasonably interpreted as encompassing essentially any protein having any function. Because "βTrcp2" is an FBP gene product, the examiner has similarly applied this broad but reasonable interpretation in construing the term "βTrcp2." MPEP 2111.01.II states, "it is important not to import into a claim limitations that are not part of

the claim." Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). If applicant intends for the claims to be so structurally and functionally limited, it is noted that MPEP 2111 makes clear that "[a]pplicant always has the opportunity to amend the claims during prosecution." Even assuming *arguendo* the claims were amended to require that all members of the genus of "FBP1" proteins share an F-box motif, it is noted that the specification acknowledges that proteins exhibiting an F-box have widely variant structures and functions (see, *e.g.*,specification at p. 2, line 20 to p. 3, line 10). Also, according to *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991), "'it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it.'" In this case, the specification and prior art acknowledge the existence of multiple FBP proteins and it is unclear as to how a skilled artisan distinguishes an "FBP1" protein from "FBP2," "FBP3," "FBP4," etc.

Accordingly, the examiner maintains the position that the specification fails to adequately describe all species encompassed by the genus of "FBP1" and "βTrcp2" proteins.

[15] The scope of enablement rejection of claims 7, 13-14, 16, and 29-36 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a prior Office action.

RESPONSE TO ARGUMENT: Applicant argues the instant specification coupled with information in the prior art provides considerable direction and guidance on how to make and use the claimed invention. According to applicant, only routine experimentation is required to make and use the full scope of claimed screening assays, which require the use of a cell expressing functionally active FBP1 and βTrcp2 proteins, which activity is "characterized by degradation of IKBα. According to applicant, the structural features of an F-box protein, along with hybridization assays, and assays for measuring FBP1 and βTrcp2 activity, enable a skilled artisan to make and use all FBP1 and βTrcp2 proteins as encompassed by the claims without requiring guidance for altering FBP1 and βTrcp2 proteins to maintain the desired function.

Applicant's argument is not found persuasive. As noted above, while applicant argues the scope of FBP1 and βTrcp2 proteins has the function of targeting IKBα for degradation and the scope of "FBP1 proteins" is structurally limited to FBP1 proteins encoded by SEQ ID NO:1, any nucleic acid encoding SEQ ID NO:2, and hybridizing variants thereof and the scope of "βTrcp2" proteins is limited to those with "minor variations," it is noted that the claims do not appear to so limit the function and structure of the scope of FBP1 and βTrcp2 proteins. Indeed, in view of the disclosure of the specification, a skilled artisan would recognize the terms "FBP1" and "βTrcp2" are neither structurally nor functionally limited. For example, the specification discloses "[f]unctionally equivalent FBP gene products may contain deletions,...additions,...or substitutions of amino acid residues within...the amino acid sequence encoded by the FBP gene" (p. 40, lines 8-10) and that "where alteration of function is desired, deletions

or non-conservative alterations can be engineered to produce altered FBP gene products. Such alterations can, for example, alter one or more of the biological functions of the FBP gene product" (p. 40, lines 20-22). According to MPEP 2111.01.I, "[d]uring examination, the claims must be interpreted as broadly as their terms reasonably allow." As such, the term "FBP1" has been broadly, but reasonably interpreted as encompassing essentially any protein having any function. Because "βTrcp2" is an FBP gene product, the examiner has similarly applied this broad but reasonable interpretation in construing the term "βTrcp2." MPEP 2111.01.II states, "it is important not to import into a claim limitations that are not part of the claim." Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). If applicant intends for the claims to be so structurally and functionally limited, it is noted that MPEP 2111 makes clear that "[a]pplicant always has the opportunity to amend the claims during prosecution." In this case, the specification discloses only a single working example of an FBP1 protein, *i.e.,* SEQ ID NO:2, and only a single working example of an βTrcp2 protein, *i.e.,* the βTrcp2 as disclosed by Kipreos and Pagano (cited in the prior Office action). Other than these working examples, the specification fails to provide guidance regarding the use of other proteins having other functions that fall within the scope of recited "FBP1" and "βTrcp2" proteins. As noted in the prior Office action and undisputed by applicant, the amino acid sequence of a polypeptide determines the its structural and functional properties. Predictability of which changes can be tolerated in a protein's amino acid sequence and

obtain the desired activity/utility requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (*i.e.*, expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. The positions within a protein's sequence where modifications can be made with a reasonable expectation of success in obtaining a polypeptide having the desired activity/utility are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, *e.g.,* multiple substitutions. At the time of the invention, methods for isolating or generating variants and mutants of a given polypeptide were known in the art. However, neither the specification nor the state of the art at the time of the invention provided the necessary guidance for altering the polypeptide of SEQ ID NO:2 with an expectation of obtaining a polypeptide having the desired activity/utility. At the time of the invention, there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity/utility. For example, the reference of Branden et al. ("Introduction to Protein Structure", Garland Publishing Inc., New York) teaches "[p]rotein engineers frequently have been surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes" and "[t]he often surprising results of such experiments reveal how little we know about the rules of protein stability... ...they also serve to emphasize how difficult it is to design *de novo* stable proteins with specific functions" (page 247). The

teachings of Branden et al. are exemplified by the reference of Witkowski et al. (*Biochemistry* 38:11643-11650), which teaches that only a single amino acid substitution results in conversion of the parent polypeptide's activity from a beta-ketoacyl synthase to a malonyl decarboxylase (see *e.g.*, Table 1, page 11647). While methods of isolating or generating variants of a polypeptide were known in the art at the time of the invention, it was not routine in the art to screen – by a trial and error process – for all polypeptides having a substantial number of modifications as encompassed by the claims for those that maintain "the activity" of SEQ ID NO:2 and/or the βTrcp2 as disclosed by Kipreos and Pagano (*supra*).

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required, undue experimentation is necessary for a skilled artisan to make and use the entire scope of the claimed invention. Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

[16] The rejection of claim(s) 7, 13-14, 16, and 29-36 under 35 U.S.C. 102(b) as being anticipated by Yaron et al. (*EMBO J* 16:6486-6494, 1997) is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a prior Office action.

RESPONSE TO ARGUMENT: Applicant argues the reference fails to teach FBP1 or *β*Trcp2 as participating in any of the methods or assays disclosed therein, fails to teach assays for detecting a change in FBP1 or *β*Trcp2 activity, and fails to teach screening methods for identifying compounds useful for treating cancer, particularly as the reference is not concerned with the interaction of FBP1 or βTrcp2 with IKBα.

Applicant's argument is not found persuasive. Addressing applicant's argument regarding the reference's alleged failure to disclose teachings regarding FBP1 or βTrcp2 or interaction thereof with IKBα, it is noted that, in order for the reference to anticipate the claimed invention, it would appear that the reference need not disclose teachings regarding FBP1 or βTrcp2 or interaction thereof with IKBα. The reference need only teach the active method steps as set forth in the method claims. The cell of Yaron et al. (1997) inherently expresses FBP1, βTrcp2, and IKBα, and inherently detects a change in FBP1 or *β*Trcp2 activity by measuring degradation of and/or phosphorylation of IKBα. See particularly MPEP 2112.II, which states, "[t]here is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference." Similarly, it would appear that the Yaron et al. (1997) reference

is not required to teach the intended use of the compounds identified in the screening methods, namely for treatment of proliferative and differentiative disorders, particularly in view of MPEP 2111.02.II, which states, "[i]f the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations, then the preamble is not considered a limitation and is of no significance to claim construction." In this case, the claims require only that the cell or cell extract comprise FBP1, βTrcp2, and IKBα and detecting a change in the activity of FBP1 or βTrcp2, including degradation of IKBα, in the presence of a test compound. That the cell or extract thereof of the Yaron et al. (1997) reference comprises FBP1, βTrcp2, and IKBα does not appear to be in dispute. It is whether or not the reference teaches detecting detecting a change in the activity of FBP1 or βTrcp2, including degradation of IKBα, that appears to be in dispute. According to applicant (instant response at p. 14, middle),

> "The instant specification teaches that E3 ubiquitin ligases, which are key enzymes involved in the ubiquitin-mediated proteolysis of proteins are comprised of three subunits: Cdc53, Skp1 and an F-box protein (FBP) and that the interaction of the E3 ubiquitin ligases with target substrates (proteins targeted for degradation) occurs via the FBP (see, e.g., the specification at p. 87, l. 27 to p. 88, l. 5). The instant specification further teaches that FBP1 and βTrcp2 are FBPs that have substrate specificity for IKBα and promote IKBα degradation (see, e.g., the specification at p. 4, ll. 22 to p. 5, ll. 26; p. 87, l. 27 to p. 88, l. 5). Thus, when FBP activity is inhibited, degradation of IKBα will be inhibited and higher levels of IKBα protein will be detected as compared to a cell with normal FBP activity. Likewise, if FBP activity is enhanced, degradation of IKBα will be enhanced and lower levels of IKBα protein will be detected as compared to a cell with normal FBP activity. The instant specification teaches that FBP1 and βTrcp2 activity can be determined by different methods, for example, detecting binding between FBP 1 and IKBα or βTrcp2 and IKBα, by detecting ubiquitination of IKBα, or by detecting a change in the protein levels of IKBα (see, e.g., the specification at p. 9, l. 31 to p. 10, l. 8; p. 91, l. 20 to p. 92, l. 3; p. 70, ll. 22 to 28)."

Thus, according to applicant, a change in the activity of FBP1 or βTrcp2 can be detected by detecting ubiquitination of IKBα and measuring a change in the protein levels of IKBα. In this case, the reference of Yaron et al. teaches a method for assaying degradation of phosphorylated IKBα protein in the presence and absence of ATP and in the presence of ATP and various peptides by measuring levels of IKBα protein by Western blotting (paragraph bridging pp. 6488-6489 and p. 6489, Figure 4). According to the results of Yaron et al., the level of phosphorylated IKBα is decreased in the presence of ATP or ATP and peptides ppFos or p21 as compared to the level of phosphorylated IKBα in the absence of ATP (compare Lanes 1 and 2 of Figure 4) and the level of phosphorylated IKBα is increased in the presence of peptides pp21 and pp19 as compared to the level of phosphorylated IKBα in the absence of peptides pp21 and pp19 (compare Lane 2 with Lanes 3 and 4 of Figure 4). Yaron et al. further teaches assaying the level of ubiquitinated phosphorylated IKBα in the presence of peptide pp19 (p. 6488, top and p. 6489, Figure 3B, compare Lanes 1 and 6) and also assaying the level of ubiquitinated phosphorylated IKBα in the presence of peptide pp21 and reticulocyte lysate fraction II (p. 6490, Figure 5A, compare Lanes 1 and 4), which resulted in an increase in ubiquitinated phosphorylated IKBα as compared to no peptide. As such, even though the reference of Yaron et al. is silent regarding FBP1 or βTrcp2, the assays of Yaron et al., by measuring levels of IKBα by Western blotting or by measuring levels of ubiquitinated IKBα, would nonetheless appear to necessarily detect a change in the activity of FBP1 or βTrcp2.

[17] The rejection of claim(s) 7, 13-14, 16, and 29-36 are rejected under 35 U.S.C. 102(b) as being anticipated by Yaron et al. (*Nature* 396:590-594, 1998; hereafter "Yaron 1998" to avoid confusion with the earlier cited Yaron et al. reference) is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in a prior Office action.

RESPONSE TO ARGUMENT: Applicant argues the reference is not directed at determining whether a compound can modulate FBP1 or βTrcp2 activity. According to applicant, the assays of Yaron et al. (1998) were performed in a cell-free system and not using a cell or cell extract as required by the claims. Applicant argues the reference fails to teach screening methods for identifying compounds useful for treating proliferative or differentiative disorders by detecting a change in FBP1 or βTrcp2 activity.

Applicant's argument is not found persuasive. Addressing applicant's argument regarding the reference's failure to disclose teachings regarding FBP1 or βTrcp2, it is noted that, in order for the reference to anticipate the claimed invention, it would appear that the reference need not disclose teachings regarding FBP1 or βTrcp2 or interaction thereof with IKBα. The reference need only teach the active method steps as set forth in the method claims. The cell of Yaron et al. inherently expresses FBP1, βTrcp2, and IKBα, and inherently detects a change in FBP1 or βTrcp2 activity by measuring degradation of and/or phosphorylation of IKBα. See particularly MPEP 2112.II, which states, "[t]here is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject

matter is in fact inherent in the prior art reference." Similarly, it would appear that the Yaron et al. reference is not required to teach the intended use of the compounds identified in the screening methods, namely for treatment of proliferative and differentiative disorders, particularly in view of MPEP 2111.02.II, which states, "[i]f the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations, then the preamble is not considered a limitation and is of no significance to claim construction." In this case, the claims require only that the cell or cell extract comprise FBP1, βTrcp2, and IKBα and detecting a change in the activity of FBP1 or βTrcp2, including degradation of IKBα, in the presence of a test compound. While applicant argues the assays of the reference do not use a cell or cell extract, applicant's attention is directed to, *e.g.,* p. 591, Figure 1 caption, which teaches the assay uses HeLa cells pre-incubated with the proteasome inhbitor ALLN and stimulated with TNF-α and p. 591, Figure 2, which teaches HeLa cell lysate treated with or without IKK. As noted above, according to applicant, a change in the activity of FBP1 or βTrcp2 can be detected by detecting ubiquitination of IKBα and measuring a change in the protein levels of IKBα. In this case, the reference of Yaron et al. teaches a method for assaying degradation of phosphorylated IKBα protein in the presence and absence of a compound by measuring levels of IKBα protein by Western blotting. As such, even though the reference of Yaron et al. is silent regarding FBP1 or βTrcp2, the assays of

Yaron et al., by measuring levels of IKBα by Western blotting, would nonetheless appear to necessarily detect a change in the activity of FBP1 or βTrcp2.

Examiner Comment/Clarification

[18] It is noted the claims have been amended to replace recitation of "Fbp1" with "FBP1." No distinction has been made between "Fbp1" as used in the specification and the term "FBP1" as recited in the claims. Put another way, the examiner interprets the term "Fbp1" to be the same as "FBP1."

Conclusion

[19] Status of the claims:

- Claims 1-7, 11, 13-14, and 16-36 are pending.
- Claims 1-6, 11, and 17-28 are withdrawn from consideration.
- Claims 7, 13-14, 16, and 29-36 are rejected.
- No claim is in condition for allowance.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Art Unit 1656